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PhRMA

July 6, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004D-0187: Draft Guidance for Industry on Premarketing Risk Assessment (69 Federal Register 25130; May 5, 2004)

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives; our members invested over $32 billion during 2003 in the discovery and development of new medicines.

Members of PhRMA share a mutual interest with FDA in bringing safer and more effective products to the market as rapidly as possible, and we embrace the importance of minimizing the occurrence of avoidable adverse events. Bringing a new drug to the market requires considerable commitment of time and resources. In order for industry to appropriately design and execute efficient drug development programs, it is important that the Agency ensure that its policies and expectations are transparent to all stakeholders, and that the standards are consistently applied. The three draft guidance documents on pre-marketing risk assessment, development and use of Risk Minimization Action Plans (RiskMAPs), and good pharmacovigilance practices represent significant progress towards these goals. When finalized, the three guidance documents will provide a good framework for the Agency and industry in their risk management efforts. PhRMA appreciates the opportunity to provide comments on the draft guidance documents.

PhRMA member companies are pleased to see that the Agency has significantly revised the guidance documents to incorporate the public input on the risk management concept papers that were published last year (68 Federal Register 11120; March 7,2003). We strongly support the development of concept papers and recommend that this approach be utilized routinely for development of major guidance documents that may precipitate extensive comments from interested parties. PhRMA agrees with and supports most of the concepts outlined in the draft guidance documents, particularly the over-arching philosophy that the ultimate goal of risk management is to ensure that risk management efforts are directed to effective processes that achieve a positive benefit/risk balance for patients. We are pleased to see increased reference to the balance between benefits and risks throughout the documents, as well as acknowledgment that RiskMAPs should be used judiciously, so as not to interfere with the delivery of benefit to the patient. This concept should also apply to pre-marketing risk assessment and post-marketing pharmacovigilance activities. Any activity beyond current

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regulatory requirements should be carefully assessed to ensure that it will provide meaningful benefit relevant to the patient population at risk, and not delay or hinder patient access to new effective therapy.

PhRMA is also encouraged to see that FDA has incorporated into all three draft guidance documents the concept that a number of different stakeholders must collaborate with industry and the Agency in risk management activities if significant improvement in the overall benefit/risk balance is to be achieved.

Since many of PhRMA's members are multinational companies, we also applaud the Agency's efforts to conform with internationally harmonized definitions and standards as much as possible. FDA guidance documents should be aligned with the approach developed by ICH and CIOMS to ensure that risk management can be a global process, as is appropriate for global products. The basic structure of risk management documents should be similar globally to allow use of the same document for all countries whenever possible. This increases the transparency and consistency of implementation of agreed post-marketing commitments. It would be useful for FDA to highlight in the guidance documents the important differences from ICH and EU guidance documents, the rationale for these differences, and the steps being taken to harmonize the differences. We believe that a global approach to pharmacovigilance and risk management is extremely important, and we strongly encourage FDA to harmonize with international consensus initiatives.

During public presentations regarding the risk management concept papers, FDA representatives have noted a diversity of information about post-marketing risk management activities that sponsors have included in marketing applications in response to new expectations derived from the FDA PDUFA 3 performance goals. PhRMA agrees with the Agency's emphasis on those few instances when, due to a serious issue, a RiskMAP is warranted. However, we believe that the Agency's expectations pertinent to the majority of marketing applications, which do not require a proposed RiskMAP, should also be addressed.

While we support most of the concepts outlined in the draft guidance documents, we are concerned that there could be a negative impact on the development of new and innovative medicines as an unintended consequence if certain concepts are applied in an inappropriate manner. Examples of such unintended consequences include requirements for pre-approval large simple safety studies that delay availability of new drug products, and RiskMAP programs that unintentionally prevent patient access to beneficial products. Indeed, burdensome RiskMAP requirements could steer patients to older products with a less favorable benefit/risk profile than one with a RiskMAP. It is critical that the FDA establishes clear transparency and consistency in the selection of products and circumstances for which additional risk assessment and risk minimization activities are requested, to ensure that patient access to new effective therapy is not jeopardized. PhRMA notes that FDA's recently issued position paper "Innovation or Stagnation - Challenge and Opportunity on the Critical Path to New Medical Products" (March 2004) highlights the increase in complexity and inefficiency of the clinical development process as a major challenge for making new medicinal products available to the public. Industry and the Agency need to work together to ensure that these risk management initiatives do not add to that complexity and inefficiency.

Comments that are specific to the Draft Guidance for Industry: Premarketing Risk Assessment are attached. Our comments on the other two draft guidance documents are submitted separately to the respective dockets.

We thank FDA for the opportunity to comment on this important topic. Please do not hesitate to contact me if any of the issues presented herein require clarification. PhRMA member companies look forward to continued dialog as the Agency proceeds with this important initiative.

Sincerely,

Allen Goldhamer

PhRMA Comments on FDA Draft Guidance for Industry: Pre-marketing Risk Assessment
Docket No. 2004D-0187

July 6, 2004

General Comments

PhRMA notes that the scope and philosophical objectives have been retained from the corresponding concept paper, and we are pleased with the Food and Drug Administration's (FDA's) obvious effort to reflect the public input it has received. We feel that the draft guidance now reflects the recognition that attempting to identify all risks prior to approval is not realistic, and the guidance now places more emphasis on a balance between benefits and risks. PhRMA also agrees with a proactive approach to anticipating safety questions and the objective of systematic risk assessment during drug development, with comparable effort and rigor as applied to assessments of efficacy.

PhRMA is pleased to see that the FDA recommends close interaction with industry to discuss potential safety concerns as drug development proceeds. It will be critical that FDA reviewers evaluate safety issues as consistently as possible between Centers and across Divisions. It is particularly important that consistency be applied in situations when FDA mandates requirements greater than that required by ICH Guidances or historically applied by FDA, in situations where a Large Simple Safety Study is required prior to approval, and in situations where FDA requires a RiskMAP at the time of initial marketing. It must also be recognized that all products are not the same, and the need for and types of risk management activities should be considered on a product-by-product basis.

While we are pleased that the FDA states that many recommendations in the guidance are not intended for all products, we do have concerns about the extent of information that may be requested on specific products.

The FDA has stated publicly that they will base decisions on data. We support that approach, but our concern is that additional studies and increased amounts of data will be required to identify as many risks as possible prior to approval, which will result in unnecessary delays in drug development and in getting needed medicines to patients.

Although there are a number of aspects of the draft guidance that are improved over the concept paper, there are several positions of concern to industry that we feel have not appreciably changed in the draft guideline including:

- Emphasis on the desirability of data from active comparator drug if "an acceptable alternative" treatment exists. PhRMA is concerned that this amounts to establishment of a new standard of approval for products that are not first in class/first therapy.
- Suggestions for situations when the size of the safety database should exceed recommendations set forth in ICH E1.
- Delaying final dose selection until Phase III will increase the size, complexity, and time to complete these trials. It will also significantly increase the probability of patients receiving an inadequate or sub-optimal dose, potentially impacting subject participation because of the additional risk of being exposed to inappropriate doses. In certain therapeutic areas, most notably anti-infectives, too low of a dose going into Phase III studies has resulted in failed development programs. Each of these considerations will contribute to delay in final delivery of effective therapy to patients.
- Requirements for including placebo arms in long-term controlled safety studies raise concerns regarding the ethical issues associated with this practice.
- The suggestion that in certain situations, large simple safety studies (LSSS) may be a prior-approval requirement or suggestions that an LSSS will be a Phase IV condition of approval.

- Non-specific proposals for pre-marketing activities by sponsors intended to reduce potential medication errors.

This guidance should also put some emphasis on the differences in individual willingness to accept risk, based on individual perception of risk and benefit. We should avoid restricting access to products where an informed patient is willing to assume the risks in order to experience the benefits, whether due to individual preference or due to severity of illness treated in a sub-population.

It would also be useful for FDA medical reviewers or risk reviewers to share good review practices and approaches with stakeholders. Communication of evolving best practices and learnings should be shared between FDA and sponsors, and ways for companies to learn from one another should be enhanced.

Specific Comments

Section: II.B. Overview of the Risk Management Guidances

Line(s)	Comment
45-51	PhRMA suggests that FDA acknowledge that formal Risk Management is an evolving field and that the value of specific risk management tools has yet to be definitively established.
56-67	PhRMA notes that FDA uses identical language in each of the three draft guidelines. Line 56 notes that many recommendations in this draft guidance are not intended to be generally applicable to all products. However, within this draft guidance, it is often unclear when the concepts should be generally applicable and when they should not. We suggest that the final guidance be specific about those expectations that should be applied to all products and criteria for determining when special considerations should apply. Adding clarity on how to determine when to incorporate specific points into a development plan will greatly enhance the value of this guidance.
65	It is not clear what is meant by an "unusual type or level of risk".

Section III. The Role of Risk Assessment in Risk Management

Line(s)	Comment
106-108	The population of patients chosen for study also affects the adequacy of risk assessment. We recommend the sentence be modified to read, "The adequacy of this assessment is a matter of both quantity....and quality (the appropriateness of the assessments performed, the adequacy of the patient populations studied and how the results are analyzed)."

Section: IV.A. Size of the Pre-marketing Safety Database

Line(s)	Comment
155 and 226	PhRMA requests that the bullets on these lines be deleted. If the size of the safety data base depends on the potential advantages of the product over existing therapy, innovation will stall for at least three reasons: (1) no one can divine all the "potential" advantages of a product at any given time – many are discovered by serendipity, others are determined in research; (2) older products may not have received sufficient scrutiny to determine their true characteristics, positive and negative, so comparisons may be impossible; (3) comparator drugs are useless to those who cannot tolerate them, so comparisons with a new drug may be

	meaningless.
160	The Agency makes reference to symptomatic treatment of non-serious diseases. Although many diseases may be viewed by some as "non-serious" they may have a dramatic impact on quality of life and in some cases are associated with disability. We suggest that the first use of the term non-serious be defined as "diseases that are not life-threatening or not associated with major irreversible morbidity".
164-173	PhRMA supports language that reflects a flexible approach to be applied when a drug is for acute use or holds promise for the treatment of life-threatening or severely debilitating illnesses. If there is evidence of clinically meaningful benefit, particularly when no suitable alternative exists, there will be a higher tolerance for risks (known and unknown). The Agency should make it clear that even small benefits to an otherwise untreated or under-treated patient population may change the acceptable risk assessment.
175	We request that the Agency clarify the definitions of "chronic use" and "short term use".
183-189	Although PhRMA believes FDA has improved the description of patients who should comprise the 1500 subjects recommended under the ICH E1 guidance, the use of the terms "relevant doses" and "reasonable representation" are vague and subject to broad interpretation. It would be helpful if FDA could be more specific or provide an illustration in order to convey useful guidance of the Agency's general expectation. It is also not clear whether the recommended size strictly refers to exposure at dosage levels intended for clinical use and whether patients exposed to dose levels lower than the intended levels could not be a part of the recommended size of exposure. Furthermore, while data from doses higher than those proposed for marketing may be informative, FDA should acknowledge that for drugs with a narrow safety margin, this practice may not be appropriate as it may put patients at increased risk for toxicity.
194	This section states that a larger safety database may provide information on late-developing adverse events. However, this would not be so much related to number of subjects as to recommended length of exposure. This type of concern may be addressed with an increase in the number of patients exposed at adequate doses for a prolonged time period (6-12 months). With regard to very late effects, the benefit/risk based on the product's known therapeutic index, indication for use, and relevant comparator profile should be considered prior to deciding that the very late adverse effect is to be evaluated before first submission.
203-206	Aggregated data from clinical trials often have insufficient power to estimate the frequency of rare events. Accordingly, issues regarding low-frequency events or SAEs may more appropriately be followed up with post-marketing activities rather than by arbitrarily increasing the size of the pre-marketing safety database. With regard to the statement that expected low-frequency adverse events must be quantified where an adverse event has been observed in similar products, PhRMA requests the agency provide examples of recent use of this approach and the outcome. Individual drug sponsors may not have access to clinical information known to FDA from other investigational drugs.
215-218	The guidance document states "...clinical trials should be designed with a sufficient number of patients to provide adequate statistical power to detect pre-specified increases over the baseline morbidity or mortality". It is unclear whether "pre-specified increases over the baseline morbidity" refers to the increases over the background rate of morbidity or within-patient changes in morbidity from baseline. In addition, PhRMA believes that the needed sample size will depend very much on what the "pre-specified increase" over the baseline morbidity or mortality is

	determined to be and that the required sample size can be very high if the increase is small. An exponential increase in the size of the safety database may not add substantially to patient safety but will add substantially to development time. Guidance on acceptable pre-specified increases in various settings is requested. Furthermore, the Agency should clarify whether a comparison with placebo would be adequate in those situations where placebo controlled trials are feasible.
220-234	PhRMA notes that FDA has retained in the draft guidance two additional situations when safety databases should be larger than described under ICH E1. Increasing the size of the database above the ICH requirement without specifically defining the concern or objective is not likely to significantly add to an assurance of patient safety. As noted above, the language on line 226 ("a safe and effective alternative...is available") is particularly problematic (i.e., since any drug requires an FDA determination of safety and efficacy to be approved). Therefore, if a drug is not the first in class or is the second treatment for a specific disease, the language would essentially mean that FDA may require a larger safety database than required under ICH E1. PhRMA is concerned that this incorporates a new standard for approval. Under the Federal Food, Drug, and Cosmetic Act, FDA must evaluate safety and effectiveness solely with respect to the drug under review. As indicated in our previous comments (line 155), we request that this bullet be deleted. The Agency should make it clear that the guidance document is not intended to change the drug product approval standard and that the sponsor is required to provide sufficient data for the Agency to conclude that the drug is safe and effective for its labeled indication. FDA's authority to consider the safety and/or effectiveness of other marketed drug products is limited to instances where a known health risk is associated with a drug class (e.g., non-sedating antihistamines) or when the applicant proposes comparative safety or efficacy claims in the product labeling. In the absence of such comparative claims, the existence of a "safe alternative" should make no difference in determining whether a larger database could be appropriate. PhRMA does not believe there is a rationale for requiring a larger database if Phase II/III studies of a new therapy demonstrated an acceptable safety and efficacy profile. The Agency should make it clear that there is no requirement to demonstrate that the test product is safer than an active comparator, and that the risk-benefit analysis is for the test product only. If FDA has contrary thoughts, the reasoning must be provided. PhRMA also requests guidance to address how many fold increase the pre-registration database will need to be if there is no specific safety signal that is being examined, i.e. how will even a 2-3 fold increase in database size be used to better define the risk of extremely rare events? The qualifying language that appears on lines 228 to 234 does not adequately address this concern. Without clear criteria for determination of a concern and a "gold standard" via therapeutic guideline, arbitrary determinations motivated by a variety of factors besides safety will be possible. An unexpected FDA opinion of this nature obtained at a pre-NDA meeting as suggested on line 234 will significantly delay development.

Section: IV.B. Considerations for Developing a Pre-marketing Safety Database

Line(s)	Comment
252-271	The draft guidance states "control groups may be given a placebo or an active comparator, depending on the disease being treated" (line 256). This is a complicated issue that needs to be carefully considered. Placebo controls in chronic diseases are often associated with ethical issues, declines in enrollment, and missing data problems due to dropouts. FDA states that the usefulness of active comparators in long-term studies depends on the adverse events of interest.

	This statement is vague and the examples provided on lines 262 through 271 do not adequately demonstrate the value of the Agency's proposed emphasis on comparative data. Since it is often not possible to detect rare events prior to approval, we suggest that FDA describe how such an approach has been successfully applied and why post-approval risk assessment activities would not be appropriate (e.g., illustrate a specific case study; describe the hypothesis tested and what definitive information was obtained). If long-term safety studies are conducted against an active comparator, FDA should not require that the sponsor power the studies for comparative safety purposes, and the guidance should reflect how these results might be described in the labeling.
279-292	PhRMA agrees with the need to broaden inclusion/exclusion criteria. However, this will also require increased sample size, as the assessment of both efficacy and safety will be more difficult because of the increased number of potential confounding factors. It should be kept in mind that there may be a trade-off between diversity and analyzability. Inclusion of diverse populations requires sufficient numbers of those patients to allow the data to be meaningful. This will have the cumulative effect of significantly increasing the number of studies and study subjects needed for drug approval. Additionally, it may not be feasible to recruit and retain such numbers in all situations. For some high-risk populations, it may not be desirable to expose subjects to a drug whose effects are not fully defined at the end of Phase II. Regarding evaluation of data on diverse populations, consideration should be given to giving a higher weight to the population in which the disease is most expressed. PhRMA suggests that FDA reconcile this guidance to the current guidance in effect for gender, race, and age diversity in a pre-registration database and add clarification as to how this will add to our knowledge in small subgroups.
307-318	PhRMA believes that dose ranging in Phase III should be considered on a case-by-case basis, based on the characteristics of the drug, disease, and Phase II findings. Using a range of doses in Phase III will: 1) result in less data on the dose that is ultimately marketed unless the trials are significantly larger; 2) significantly increase the size of Phase III programs if we want to maintain reasonable power in comparing efficacy between doses and the comparator; 3) potentially lead to requests for multiplicity adjustment because of the inclusion of multiple doses for efficacy evaluations; and 4) result in more three- or four-armed Phase III studies, requiring a dramatic increase in subjects. As a result, Phase III dose ranging requirements would not only increase the time and complexity of product development, but would also expose more clinical trial subjects to potentially inadequate doses (in a balanced four arm study, only one in four patients would receive the potentially optimal dose). Similarly, examination of exposure-response relationships in Phase III should be undertaken on a case by case basis and in general should only be undertaken when there is sufficient evidence that the range of expected exposures in the trial would be sufficient to define an exposure-response relationship. A promising tool emerging from dialog between FDA and industry regarding innovative methods for achieving comprehensive dose-response evaluation early in the drug development continuum is the adaptive Phase II study design approach, which involves the dynamic/continual evaluation of a broad spectrum of doses within a single Phase II clinical trial. Although flexible dosing does not allow for a formal comparison between doses, it does allow patients and their physicians to find the dose that works the best for the patients. This, and other potential

	approaches to dose evaluation, are the intended focal point of discussions being piloted in the context of the Phase IIa meeting and is the subject of a planned FDA guidance. Lines 316-318 state that demonstrating a dose-response relationship in late phase clinical trials could add important information to the assessment of efficacy. PhRMA believes that late phase clinical trials are generally too late in the development process to examine dose-response relationship. By this time, adequate dose-response examination should have been performed and the final dose(s) selected for commercialization.

Section: IV. C. Detecting Unanticipated Interactions as Part of a Safety Assessment

Line(s)	Comment
342-343	While PhRMA recognizes the potential value of understanding product-disease interactions, the reality of determining these in a practical manner is clearly a challenge. Examples would prove useful in this section, be it for variability in disease state or in concurrent diseases (presumed here to mean not the disease under study). Product-disease interactions are most important for the treatment indication. To obtain more information on effects of concurrent disease, broader (Phase III) inclusion criteria should allow for sufficient variability in and prevalence thresholds of concomitant diseases within the epidemiology of the intended final population.
345	There are a myriad of dietary supplements in commerce, including some that have been associated with significant adverse effects, either alone or in combination with prescription drugs. Such products do not require a prescription and it is difficult to know what products are "commonly used" by prospective patients, or "likely to be co-administered". PhRMA recommends deleting this point.
356-361	PhRMA suggests that reference to population pharmacokinetics (PK) make it clear that data should be obtained via a directed investigation with planned objectives and analyses. *Post hoc* analyses (for unanticipated adverse events or drug interactions) are problematic for a number of reasons including a disassociation with the actual PK evaluation and the event (adverse event, concomitant medication, etc.); appropriate data collection with well-timed blood sampling and dosing information. Additionally, the increased complexity of including these investigations is not trivial nor is the impact on the feasibility of conducting such studies including PK analyses. There should be clearly defined criteria when population PK approaches are relevant/needed, to avoid having the expectation that every study would include a PK component.
363	To be consistent with other recent FDA guidelines, we suggest that this sentence be revised to state "...one or more well-established and known valid biomarkers pertinent..." This clarity is needed to avoid confusion in cases where a sponsor is developing a potential safety biomarker.

Section: IV. D. Developing Comparative Safety Data

Line(s)	Comment
368-397	As a general matter, PhRMA objects to FDA's statement that comparative safety data would be desirable in a variety of situations. While PhRMA recognizes that FDA has prefaced this by stating that comparative safety trials "generally are not necessary," PhRMA nevertheless is concerned that the general discussion could encourage FDA to request comparative trials on a more routine basis. As discussed in our general comments, this would represent a new standard for approving drug products that goes beyond the statutory requirements. We thus suggest removing this section.

	The encouragement of comparative trials infers that such trials would allow an accurate assessment of relative risk. This is not necessarily true as clinical trials are powered to meet primary efficacy objectives. In the case where comparative efficacy claims are sought, as suggested in lines 393-397, the sample size may not be adequate to characterize adequately the safety advantages or disadvantages. Furthermore, it should not be the expectation that studies for comparative efficacy claims be powered to demonstrate both efficacy and safety objectives, as this has the potential to substantially increase the size, complexity, and cost of individual studies. The draft guidance suggests that if there is a well-established related therapy, comparator trials would be desirable in certain situations. The guidance should reflect that when there are diseases or categories of drugs where FDA feels that a specific public health objective can be realized by conducting comparative trials, the Agency should develop a specific guidance applicable to the disease and/or therapeutic class. This will allow for transparency of the criteria applied, allow for public input from scientific experts as part of the guidance development, ensure that consistent requirements are applied to all sponsors, and facilitate predictable development plans. The guidance should describe the Agency's expectations regarding statistical design features of comparator trials that would achieve the objective intended by this section. On line 376, the Agency's intent with respect to characterizing background rates is not clear. As written, this could mean morbidity associated with the natural history of the disease, co-morbidities, or morbidity associated with concomitant therapies. On lines 378 to 380, FDA suggests that results from a single-arm study with a high rate of adverse events would suggest the need for a three-arm trial of the investigational drug compared to a comparator and placebo. We question the value of this approach if the sponsor has conducted placebo-controlled trials, and epidemiological studies or other data sources have established the background rate of co-morbidities or adverse events associated with alternative treatment options. PhRMA suggests that the second bullet ("there is a well-established related therapy") be deleted. Even if there is a well-established therapy, there will always be a subset of the population for whom the well-established therapy is not useful and the new therapy may be useful. Mandating comparison to the well-established therapy raises the bar for new products, resulting in inhibition of innovation. In the event that this bullet is retained, we suggest that the language on line 382 be changed to: "There is an alternative treatment available with a well-established benefit-risk profile." There are many "well established" therapies that have not been proven to be efficacious via controlled clinical trials. The Agency should describe how safety information from comparative safety studies could be described in product labeling.

Section: V. Special Considerations for Risk Assessment

Line(s)	Comment
402-559	The recommendations in this section are broad and could result in a substantial increase in study requirements for individual drugs. We suggest that requests for such studies be based on specific risks and clear areas of public health concern. In addition, it should be clear that such data would be critical to make better decisions about patient safety. PhRMA notes that this section begins by stating that some risk assessment issues would apply only in certain circumstances (lines 402-404), however the topics within

	the section are all given very general titles (e.g., Risk Assessment During Product Development, Safety Aspects that Should be Addressed During Product Development) which do not seem to be describing requirements that would only apply in certain circumstances. There are always resources to consider when drug development programs are planned. The costs of any new requirements must be weighed carefully against potential benefits. If generally applied, these recommendations would increase the number and/or complexity of studies required. The significant increase in the cost of drug development would not necessarily deliver an increase in understanding of product safety.

Section: V. A. Risk Assessment During Product Development

Line(s)	Comment
434-441	FDA suggests that sponsors consider reserving blood samples in Phase III studies for possible retrospective testing for various biologic assessments, including pharmacogenomic markers, immunogenicity, or other biomarkers. Currently, an increasing number of Phase III trials include the conduct, in a "prospective" manner, of pharmacogenetic tests with appropriate informed consent. Rate of participation is often low. PhRMA is concerned that participation may be even lower, and could result in a less diverse study population, due to ethical or legal concerns (because of HIPAA regulations, a different consent form is likely to be required) if patients are asked to consent for tests to retrospectively determine a pre-determined or undetermined number of markers that may or may not be eventually performed. In addition, for international studies there are conflicting national rules governing obtaining and using reserved blood samples that reflect national policies on privacy and informed consent. The guidance document should acknowledge these potential limitations/issues.
443-463	A pre-approval requirement of a large simple safety study (LSSS) is a significant burden that should be reserved for only those cases when a signal suggests a possible serious adverse event that if substantiated would result in a significant public health risk and prevent product approval. A pre-approval requirement for an LSSS is not a trivial requirement as it represents a *de facto* fourth phase to development. It would be difficult to design an LSSS study until evidence of efficacy in Phase III had been obtained. On line 450, FDA indicates that an LSSS is most commonly performed as a Phase IV commitment, but then goes on to describe possible reasons for conducting a pre-approval LSSS (lines 454 to 463). No examples of when a post-approval LSSS might be considered are outlined. Conducting an LSSS is a significant commitment at any stage of the product life-cycle. In addition, we suggest that the first sentence of the paragraph that begins on line 460 be revised to read: "When there are early signals (i.e., pre-clinical or clinical) of serious toxicities or other unique or special considerations (e.g., regarding the safety of the use of the product with a concomitant medication where the previous clinical data have not addressed the issue sufficiently) that are not likely to be sufficiently resolved by the available data and are unlikely to be sufficiently addressed by the remaining ongoing studies". We also request that FDA include a reference that describes considerations for LSSS design features consistent with current FDA expectations.

Section: V.B. Risk Assessment and Minimizing the Potential for Medication Errors

Line(s)	Comment
473-517	The guidance is requesting an extensive pre-marketing risk assessment regarding

	possible medication errors. It is not clear if this is a request for development programs generally or if this would be only for certain circumstances or types of products. Potential medication errors were discussed in detail in the industry comments to the FDA regarding the March 2003 proposed safety reporting regulations (the "Safety Tome"). There is an issue with definition since the current regulations include only adverse event definitions for specific patients and events, not hypothetical situations such as confusion over drug names. In addition to the comments we submitted on the "Safety Tome", we think it is important to highlight that it is not appropriate for FDA to attempt to effect changes in existing regulatory standards via guidance documents. In addition, this guidance is not the appropriate vehicle to deal with specific details surrounding medication error prevention analysis (MEPA). A more appropriate vehicle for presenting Agency recommendations on this subject would be the "specific and expanded guidance on medication error prevention analysis" referenced in text lines 512 and 513. This would help ensure regulatory consistency across various guidance documents that deal with medication errors. This guidance document and plans for the guidance on medication error prevention analysis (MEPA) appear to ignore the recommendations from the December 4, 2003 meeting of the Drug Safety and Risk Management Advisory Committee, which recommended delaying issuance of a guidance until appropriate outcomes data could be developed. Indeed, it goes well beyond the uncertainties of trademark evaluation discussed on December 4 into risk factors surrounding the established names, container label, carton labeling, patient/consumer labeling, professional package insert labeling, and packaging. Evaluation techniques to determine potential medication error risks for most of these items have not been developed or validated. In the event that the Agency decides to include text on MEPA in this document, our specific comments and edit suggestions are outlined in the following paragraphs.
482	This statement should be edited to exclude the word "known" since sponsors can not identify known medication errors in the pre-marketing phase.
483-484	This statement should be modified to replace "trade names" with "trademarks," replace the word "written" with the word "spelling," and replace the word "spoken" with the word "pronunciation." PhRMA draws FDA's attention to the language in 21 CFR 201.10(c)(5) that refers to similarities in "spelling or pronunciation." Experience has shown that similarities in "written" trademarks introduces a wide range of hand writing distortions that can make any trademark appear similar to other trademarks, even those that share no similarity when spelled. Determining similarities in "written" trademarks requires subjective judgment with no established standards for guidance. Further, the guidance should not introduce language that goes beyond the existing regulations.
495	The reference to "clinical trials" should be deleted from the list of techniques that can be employed to assess the potential for medication errors.
500-510	Sponsors have an interest and role to play in the development of established names; however, it will require a new collaborative approach to apply risk assessment techniques. The sponsor-controlled MEPA techniques for trademark evaluation would not be appropriate for established names for the following reasons: • They do not factor in the negotiation and approval process at the USAN Council and the INN Committee of the WHO. • The established name must contain stem similarity to accomplish its communication goals. • Key elements of clinical use, such as dosage form, dosage strength, dosage

	regimen, and therapeutic indications are often not known until after the approval of the established name.
512	Although FDA acknowledges that a more complete guidance addressing MEPAs is under development, it would be helpful if this document provided specific reference to literature citations that more fully explain the concepts and proposed activities described on lines 493 to 498, as evaluation techniques to determine potential medication error risks for the areas described in this document (lines 482 – 488) have not been developed or validated.

Section: V.C. Safety Aspects that Should be Addressed During Product Development

Line(s)	Comment
519-559	PhRMA is concerned that the proposed guidance states that all drug development programs should include assessments for QTc prolongation, liver toxicity, drug-drug interactions, polymorphic metabolism, as well as two new additions, nephrotoxicity and bone marrow toxicity. It is somewhat reassuring that the proposed guidance states that addressing these would not always involve the generation of data, but it is not explained when pre-clinical studies or other data could be appropriate. We suggest that the clarifying language, "as appropriate" be added to the introductory sentence in this section (line 521). PhRMA recommends that there be a discussion about these potential issues during drug development, but that there not be an absolute requirement for such assessments.

Section: VI. Data Analysis and Presentation

Line(s)	Comment
564-567	This section should also include reference to the ICH Guidance for Industry M4E. PhRMA believes this document, combined with ICH E3, has effectively superseded FDA's 1988 guidance and contains the most current information on how clinical safety data should be integrated, organized and presented in NDAs. It is our assumption that the new considerations related to coding, temporal associations and dose effect would be best addressed within the Summary of Clinical Safety in Module 2 of a CTD formatted NDA. The Agency should consider ICH E2E during development of FDA guidances to allow for harmonization and streamlining of risk management activities and deliverables.

Section: VI.A. Describing Adverse Events to Identify Safety Signals

Line(s)	Comment
569	This section focuses exclusively on clinical AEs. PhRMA suggests it would be worthwhile to also address adverse events measured by laboratory parameters and other biomarkers.
581	PhRMA assumes that although the guidance states that sponsors should use one coding convention or dictionary throughout a clinical program, this takes into account updating the MedDRA dictionary as new versions become available. We would appreciate confirmation of this assumption.
603	PhRMA requests that FDA provide clarification regarding whether consultation with the FDA to re-characterize an event to make it consistent with accepted case definitions should be conducted "real-time" or as a group review at the time of integrated analysis of a clinical trial or development program.
640-675	The relative strengths and weaknesses of "splitting" versus "lumping" coding practices are well described. To some extent, MedDRA already contains some pre-specified groups that are searchable using the special search term facility. One of

	the challenges with pre-specified groups is that they need to be reconsidered with every MedDRA version change. Furthermore, to make "constellations" or "groups" of certain adverse events useful and interpretable, uniformity is needed for drugs in the same class and perhaps, for drugs across classes. PhRMA suggests that this is something that can be built into MedDRA, and that FDA should establish and make publicly available groupings of MedDRA terms that would serve as case definitions for commonly reviewed signals and adverse events. Since prescribers often rely on package inserts to compare products for similar pharmacologic effects, it will be useful to have similar types of groupings in the PIs to facilitate comparisons.
662-664	Examples from FDA of grouping approaches using MedDRA would be helpful for industry.

Section: VI.B. Analyzing Temporal or Other Associations

Line(s)	Comment
690-691	Because there are many occasions where increasing event rates do not suggest causality, and there are occasions where causally related adverse event rates decrease over time as indicated on line 698-699, we suggest that the example "(e.g., an increasing rate of events over time could suggest causality)" be deleted.

Section: VI.C. Analyzing Dose Effect as a Contribution to Risk Assessment

Line(s)	Comment
756	While "cut point" analyses appear to be useful there may not be enough patients in the border zones to permit valid statistical analyses.

Section: VI.E. Using Pooled Data during Risk Assessment

Line(s)	Comment
806-811	There are areas where placebo-controlled studies are not ethical and all randomized trials employ active comparators. It would be helpful to mention the pooling principles for such areas.

Section: VI.F. Rigorous Ascertainment of Reasons for Withdrawals from Studies

Line(s)	Comment
864-870	While PhRMA agrees with the objective of rigorous ascertainment of reasons for withdrawal from studies, the language in this section appears to presume that sponsors will have ongoing access to follow-up information for subjects who choose not to participate. Despite best efforts this may not be the case, even in situations when withdrawal was the result of an adverse event (e.g., in cases of threatened litigation), further requests for follow up information may be denied. The draft guidance should reflect that follow-up information should be diligently pursued but if access is denied or not possible, the sponsor's efforts should be recorded in the case report forms.

Section: VI.H. Important Aspects of Data Presentation

Line(s)	Comment
897-898 and footnote 12 (referenced in line 887)	Reference to the 1988 guidance should be replaced by reference to the 2001 CTD guidance. FDA has indicated in other fora that the information previously contained in an ISS may now be addressed within the Summary of Clinical Safety in Module 2, and that an ISS will not be routinely required. In addition, it may not be possible for the sponsor to "fully characterize" the adverse event profile of other drugs in that class. We recommend that the sentence "For a drug that is a new member..." be replaced by "For drugs that are new members of an existing class of drugs, the

	Summary of Clinical Safety or Integrated Summary of Safety should include a discussion of the known adverse event profile of the class and how this knowledge was used to enhance the development of the new compound".
897-899	In addition to reference to the integrated summary of safety (ISS), the guidance should also refer to the appropriate section within module 2 of the CTD when such an application does not contain an ISS.
920-925	This section indicates that CRFs of subjects who died or discontinued prematurely due to an adverse event should include hospital records, autopsy reports, biopsy reports and radiological reports. The reasons are compelling; however, implementation is difficult to achieve in the current healthcare environment, be it in the US or Rest of World, due at least in part to privacy considerations (HIPAA, etc).